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STEREOSPECIFIC TOTAL SYNTHESES OF THE THREE DIASTEREOISOMERS OF CYCLOEUDESMOL[1)]

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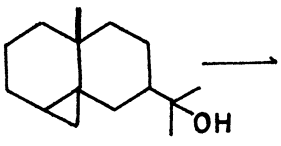
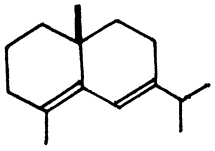
The stereospecific total syntheses of the three diastereoisomers of cycloeudesmol (Ia, Ib, and Ic) were carried out with the object of establishing the structure of cycloeudesmol.

Cycloeudesmol (I) was isolated by Fenical and Sims from the marine alga Chondria Oppositiclada Dawson[2)] and was shown to be antibiotic toward Staphylococcus aureus and Candida albicans. The structure of this compound was proposed as shown in structure (I) on the basis of spectral data and its acid-catalyzed transformation to (+)-δ-selinene (II). Since the stereochemistries of the cyclopropyl and 1-hydroxy-1-methylethyl moieties of I are not clear, four stereoisomers (Ia, Ib, Ic, and Id) are possible for its structure. Recent



I



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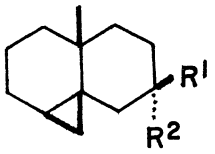
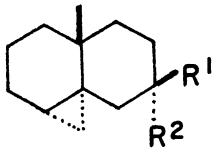


Ia $R^1=C(CH_3)_2OH$, $R^2=H$
Ib $R^1=H$, $R^2=C(CH_3)_2OH$



Ic $R^1=C(CH_3)_2OH$, $R^2=H$
Id $R^1=H$, $R^2=C(CH_3)_2OH$

communication of the syntheses of the β-cyclopropyl isomers (Ia and Ib) by Moss et al.[3)] prompted us to report our independent results of the stereospecific total syntheses of the three diastereoisomers of cycloeudesmol (Ia, Ib, and Ic).

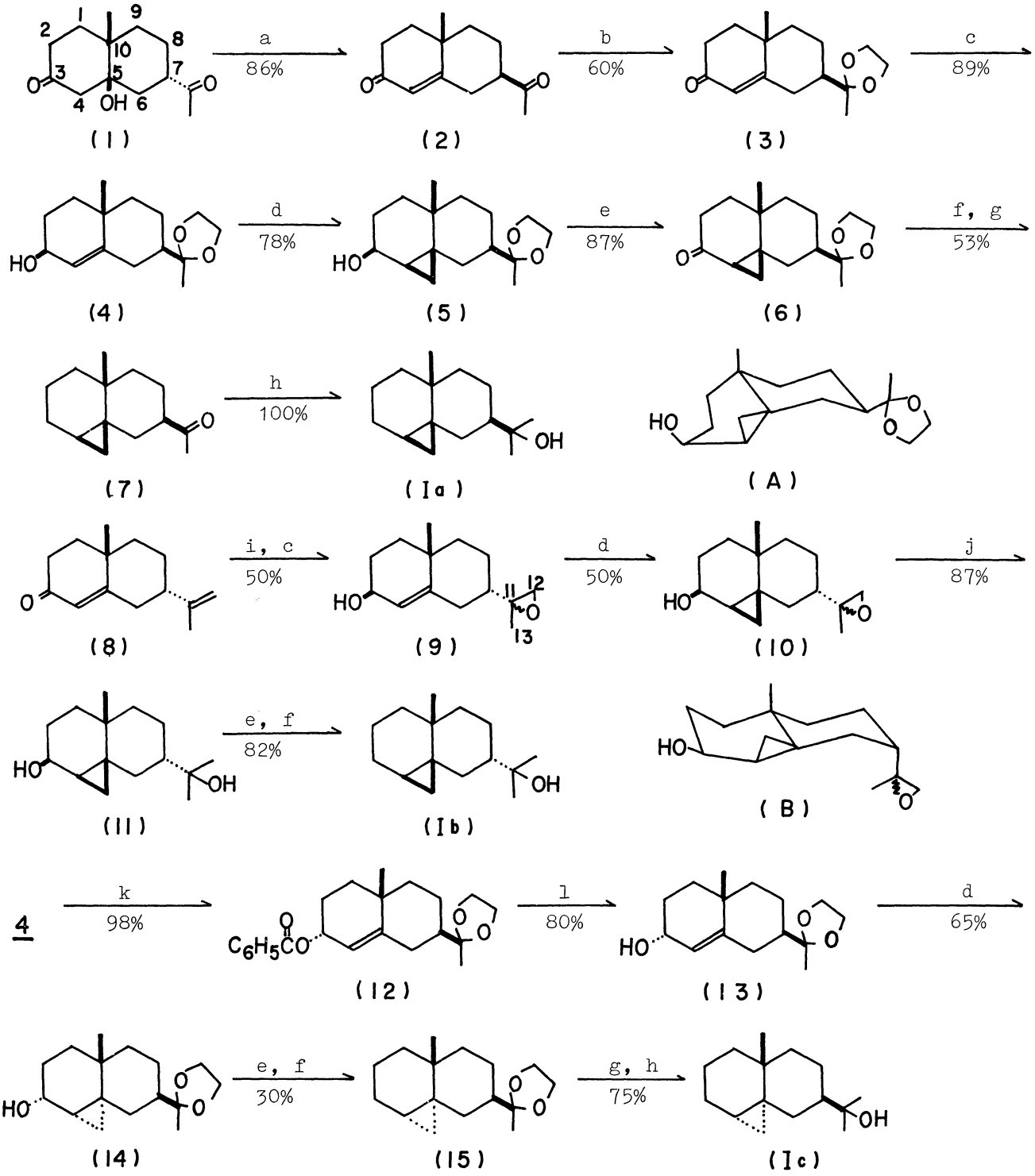
The starting material of our synthesis of Ia is a diketone (2) which was prepared from a ketol (1) under acidic conditions.[4)] Selective acetalization of the saturated carbonyl group of 2 with 1.2 equiv of ethylene glycol gave a ketoacetal (3). Reduction of 3 with $LiAl(t\text{-}BuO)_3H$ afforded a 3β-alcohol (4) [NMR

($CDCl_3$): δ 4.18 (1H, broad d, J=9.0 Hz, C_3-H), 5.36 (1H, m, $W_{h/2}$=5.0 Hz, C_4-H)].[5] The Simmons-Smith reaction of 4 gave a β-cyclopropyl derivative (5) [NMR ($CDCl_3$): δ 0.14 (1H, dd, J=5.0 and 8.5 Hz, cyclopropyl $>C<^{H}_{H}$), 0.64 (1H, dd, J=5.0 and 5.0 Hz, cyclopropyl $>C<^{H}_{H}$), and 4.34 (1H, dddd, $J_{3\alpha,4\alpha}$=6.0, $J_{3\alpha,2\alpha}$=5.0, $J_{3\alpha,2\beta}$=1.0 and $J_{3\alpha,1\alpha}$=1.0 Hz, C_3-H)]. The stereochemistry of 5 was determined as shown in structure (A) on the basis of the reaction mechanism of the Simmons-Smith reaction to the cyclic allyl alcohols[6] and the analysis of the NMR spectrum. Oxidation of 5 by the Collins procedure afforded a ketone (6) [IR (CCl_4): 1685 cm^{-1}]. The Wolff-Kishner reduction of 6 and successive deacetalization gave a ketone (7). Treatment of 7 with methylmagnesium iodide afforded Ia, mp 75°C [MS (25 eV): m/e 222 (M^+), 204 (M^+-H_2O); NMR (CCl_4): δ 0.03-0.75 (3H, m), 0.98 (3H, s), 1.09 (3H, s), and 1.11 (3H, s)], which was clearly different from natural cycloeudesmol in the NMR spectrum in CCl_4.[2]

The starting material of our synthesis of Ib is an α,β-unsaturated ketone (8).[7] Epoxidation of 8 with m-chloroperbenzoic acid and successive reduction of the resulting epoxy ketone with $LiAl(t\text{-}BuO)_3H$ gave a 3β-alcohol (9)[8] [NMR ($CDCl_3$): δ 4.17 (1H, broad d, J=9.0 Hz, C_3-H) and 5.33 (1H, m, $W_{h/2}$=6.0 Hz, C_4-H)]. The Simmons-Smith reaction of 9 gave a β-cyclopropyl derivative (10)[8] [NMR ($CDCl_3$): δ 0.16 (1H, dd, J=5.0 and 8.5 Hz, cyclopropyl $>C<^{H}_{H}$), 0.56 (1H, dd, J=5.0 and 5.0 Hz, cyclopropyl $>C<^{H}_{H}$), and 4.16 (1H, ddd, $J_{3\alpha,4\alpha}$=5.0 Hz, $J_{3\alpha,2\alpha}$=5.0 Hz, and $J_{3\alpha,2\beta}$=9.0 Hz, C_3-H)] whose stereochemistry was shown in structure (B).[6] Reduction of 10 with $LiAlH_4$ afforded a diol (11). Oxidation of 11 and the successive Wolff-Kishner reduction gave Ib as an oily substance [NMR (CCl_4): δ 0.00-0.30 (2H, m), 0.61-0.82 (1H, m), 0.92 (3H, s), 1.095 (3H, s), and 1.10 (3H, s)], which was clearly different from natural cycloeudesmol in the NMR spectrum in CCl_4.[2]

Since the two β-cyclopropyl derivatives, Ia and Ib, were not identical with cycloeudesmol, we chose an α-cyclopropyl derivative (Ic) as a next target. We envisioned an approach which consisted of the inversion of β-hydroxyl group of 4 to α-hydroxyl group and successive Simmons-Smith reaction to the resulting α-alcohol (13) for the stereospecific introduction of α-cyclopropyl moiety.[6]

Treatment of 4 with benzoic acid in the presence of triphenylphosphine and diethyl azodicarboxylate[9] gave a benzoate (12). Hydrolysis of 12 with 2M KOH in MeOH afforded the desired α-alcohol (13) [NMR ($CDCl_3$): δ 4.08 (1H, m, $W_{h/2}$=8.0



a: conc HCl, AcOH, room temp, 26 h; b: 1.2 eq [OH, OH, p-TsOH, C_6H_6, ref; c: $LiAl(t\text{-}BuO)_3H$, THF, ref; d: Zn(Cu)-CH_2I_2, ether-DME, 10°C; e: $CrO_3 \cdot 2Py$, CH_2Cl_2, 0°C; f: $NH_2NH_2 \cdot H_2O$, KOH, DEG, 120°C(1 h), 180°C(3 h); g: 20% aq AcOH-EtOH, ref; h: MeMgI, ether, room temp; i: m-$ClC_6H_4CO_3H$, CH_2Cl_2, 0°C; j: $LiAlH_4$, ether, room temp; k: $(C_6H_5)_3P$, $C_6H_5CO_2H$, $C_2H_5O_2C\text{-}N{=}N\text{-}CO_2C_2H_5$, THF, room temp; l: 2M-KOH, MeOH, 40°C.

Hz, C_3-H) and 5.50 (1H, d, J=5.0 Hz, C_4-H)]. The Simmons-Smith reaction of 13 gave an α-cyclopropyl derivative (14) [NMR ($CDDl_3$, 60 MHz): δ 0.17 (1H, dd, J=5.0 and 9.0 Hz, cyclopropyl $>C<^{H}_{H}$), 0.77 (1H, dd, J=5.0 and 5.0 Hz, cyclopropyl $>C<^{H}_{H}$), and 4.40 (1H, m, $W_{h/2}$=8.5 Hz, C_3-H)] stereoselectively.[6),10)] Oxidation of 14 by the Collins procedure and the successive Wolff-Kishner reduction of the resulting ketone gave an acetal (15). Deacetalization of 15 and successive treatment of the resulting ketone with methylmagnesium iodide gave Ic as a crystalline material [MS (25 eV): m/e 222 (M^+), 204 (M^+-H_2O); NMR (CCl_4): δ 0.00-0.85 (3H, m), 1.08 (3H, s), and 1.11 (6H, s)], which was clearly different from natural cycloeudesmol in the NMR spectrum in CCl_4.[2)]

Since Ia, Ib, and Ic are different from cycloeudesmol, the structure of cycloeudesmol might be represented by Id with the α-cyclopropyl and α-1-hydroxy-1-methylethyl moieties. Efforts directed to the syntheses of cycloeudesmol (Id) are now in progress.

References and Notes

1) Preliminary reports were presented at the 21th TEAC, Tokushima, November, 1977 (ab., p 288) and the 22th TEAC, Yokohama, October, 1978 (ab., p 235).
2) W. Fenical and J. J. Sims, Tetrahedron Lett., 1974, 1137.
3) R. A. Moss, E. Y. Chen, J. Banger, and M. Matsuo, Tetrahedron Lett., 1978, 4365.
4) D. C. Humber, A. R. Pinder, and R. A. Williams, J. Org. Chem., 32, 2335 (1967).
5) NMR spectra were recorded on a Varian HA-100 spectrometer unless otherwise stated.
6) W. G. Dauben and G. H. Berezin, J. Am. Chem. Soc., 85, 468 (1963).
7) J. A. Marshall and H. Roebke, J. Org. Chem., 33, 840 (1968).
8) The compounds (9) and (10) are a 1:3 mixture of diastereoisomers at C_{11}.
9) O. Mitsunobu and M. Eguchi, Bull. Chem. Soc. Jpn., 44, 3427 (1971); A. K. Bose, B. Lal, W. A. Hoffman III, and M. S. Manhas, Tetrahedron Lett., 1973, 1619; S. Masamune and D. W. Brooks, Tetrahedron Lett., 1977, 3239.
10) The α-orientation of newly introduced cyclopropyl moiety of 14 was also supported by the fact that the oxidation product of 14 by the Collins procedure was different from 6.

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